Therapeutic Class Overview
Ulcerative Colitis Agents

Therapeutic Class

- **Overview/Summary:** Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer.[3] Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology and presentation. Ulcerative colitis is limited to the rectum and colon, and affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] The 5-aminosalicylic acid (5-ASA) derivatives available in oral formulations include balsalazide, mesalamine, olsalazine and sulfasalazine. Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[4-17] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol®, Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at a higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[4-18] Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[19]

Table 1. Current Medications Available in the Class[4-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Treatment of mildly to moderately active UC in patients ≥5 years of age (Colazal®), treatment of mildly to moderately active UC in male patients ≥18 years of age (Giazo®)	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)	✔
Mesalamine (Apriso®, Asacol®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Induction of remission in adults with active, mild to moderate UC (Lialda®), induction of remission and for the treatment of patients with mildly to moderately active UC (Pentasa®), maintenance of remission of UC in adults (Apriso®, Lialda®), treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis (Rowasa®, SfRowasa®), treatment of mildly to moderately active UC and for the maintenance of remission of UC (Asacol®, Delzicol®), treatment of mild to moderately active ulcerative proctitis (Canasa®), treatment of moderately active UC (Asacol® HD)	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 400 mg (Asacol®) 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 375 mg (Apriso®) 500 mg (Pentasa®)	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Rectal enema: 4,000 mg/60 mL unit (Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)	
Olsalazine (Dipentum®)	Maintenance of remission of UC in patients who are intolerant of sulfasalazine	Capsule: 250 mg (Dipentum®)	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Prolongation of the remission period between acute attacks of UC (Azulfidine®, Azulfidine EN-tabs®), treatment of mild to moderate UC, and as adjunctive therapy in severe UC (Azulfidine®, Azulfidine EN-tabs®), Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs, (Azulfidine EN-tabs®) and treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs] (Azulfidine EN-tabs®)	Delayed-release tablet: 500 mg (Azulfidine EN-tab®) Tablet: 500 mg (Azulfidine®)	✔

NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- A Cochrane review of the 5-aminosalicylic acid (5-ASA) derivative oral preparations for the induction of remission in patients with ulcerative colitis, demonstrates that newer 5-ASA derivatives are significantly more effective compared to placebo with no statistically significant differences between 5-ASA preparations.[20]
- Results from a meta-analysis comparing mesalamine once daily to multiple daily dosing demonstrated that once-daily dosing is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of ulcerative colitis. In addition, once-daily dosing is more effective for inducing remission in active ulcerative colitis compared to multiple daily dosing.[21]
- Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal ulcerative colitis.[22]
- In another meta-analysis, rectal 5-ASA was significantly more effective compared to placebo and rectal corticosteroids for inducing remission in ulcerative colitis. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[23]
- A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[24]
- In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy was more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active ulcerative

colitis. Moreover, intermittent topical 5-ASA therapy was more effective compared to oral 5-ASA therapy for preventing relapse of quiescent ulcerative colitis.[25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current guidelines by the American College of Gastroenterology, oral aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease.[26]
  - Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents more effective compared to each agent alone.[26]
  - Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is better than oral mesalamine alone. [26]
  - Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission. [26]
- Other Key Facts:
  - Balsalazide and sulfasalazine oral formulations are available generically.[19]
  - Topical mesalamine enemas are available generically.[19]

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Therapeutic Class Review
Ulcerative Colitis Agents

Overview/Summary

Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer. Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology. As a result, the approach to the treatment of each condition may differ.[3] Ulcerative colitis is limited to the rectum and colon and generally affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] Ulcerative colitis almost always involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon. Ulcerative proctitis refers to disease limited to the rectum. Ulcerative proctosigmoiditis refers to disease limited to the rectum and sigmoid colon and not involving the descending colon. Left-sided or distal ulcerative colitis is defined as disease that extends beyond the rectum and as far proximally as the splenic flexure. Extensive colitis refers to disease extending proximal to the splenic flexure but sparing the cecum. Pancolitis is used when the inflammatory process extends beyond the splenic flexure to the cecum.[3]

The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] Treatments that work to relieve the inflammatory process include tumor necrosis factor inhibitors, antimicrobials, corticosteroids, immunosuppressive agents and salicylates. The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] According to current guidelines by the American College of Gastroenterology, oral 5-aminosalicylic acid (5-ASA) derivatives (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease. Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents is more effective than each agent alone. Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is more effective than oral mesalamine alone.[4] Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission.[4]

Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[5-18] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol®, Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at the higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[5-19] The specific Food and Drug Administration-approved indications of the oral 5-ASA derivative preparations are listed in Table 2. Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[20]

Medications

Table 1. Medications Included Within Class Review[5-18]

Generic Name (Trade name)	Medication Class	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Inflammatory bowel agents	✔
Mesalamine (Apriso®, Asacol®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Inflammatory bowel agents	✔
Olsalazine (Dipentum®)	Inflammatory bowel agents	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Inflammatory bowel agents	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[5-18]

Indication	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Induction of remission in adults with active, mild to moderate UC	-	✔ (Lialda®)	-	-
Induction of remission and for the treatment of patients with mildly to moderately active UC	-	✔ (Pentasa®)	-	-
Maintenance of remission of UC in adults	-	✔ (Lialda®, Apriso®)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	✔	-
Prolongation of the remission period between acute attacks of UC	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	✔ (Rowasa®, SfRowasa®)	-	-
Treatment of mildly to moderately active UC and for the maintenance of remission of UC	-	✔ (Asacol®, Delzicol®)	-	-
Treatment of mildly to moderately active UC in male patients ≥18 years of age	✔ (Giazo®)	-	-	-
Treatment of mildly to moderately active UC in patients ≥5 years of age	✔ (Colazal®)	-	-	-
Treatment of mild to moderately active ulcerative proctitis	-	✔ (Canasa®)	-	-
Treatment of mild to moderate UC, and as adjunctive therapy in severe UC	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Treatment of moderately active UC	-	✔ (Asacol® HD)	-	-
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs	-	-	-	✔ (Azulfidine EN-tabs®)

Indication	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]	-	-	-	✔ (Azulfidine EN-tabs®)

NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis

Potential off-label uses of mesalamine include Crohn's disease and Reiter's disease. Sulfasalazine may potentially be used off-label for radiation-induced disorders of the gastrointestinal tract.[21]

Pharmacokinetics

Table 3. Pharmacokinetics[5-18]

Generic Name	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Balsalazide	Minimal	<1	5-ASA	1*
Mesalamine	20 to 30	13 to 30	N-acetyl-5-ASA	7 to 12†; 9 to 10‡
Olsalazine	1 to 3	0.3 to 0.9	5-ASA	0.9
Sulfasalazine	<15	Variable	5-ASA and sulfapyridine	7.6±3.4

5-ASA=5-aminosalicylic acid.
*Metabolite.
†Delayed-release tablet.
‡Extended-release capsules.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the 5-aminosalicylic acid (5-ASA) preparations for their respective Food and Drug Administration-approved indications are outlined in Table 4.[22-40]

The results of a trial comparing Asacol® (mesalamine) 2.4 g/day to Asacol® HD (mesalamine) 4.8 g/day demonstrated that treatment success at six weeks was not statistically different between the treatment groups in patients with mild to moderately active ulcerative colitis (UC). In addition, 51% of patients treated with Asacol® (mesalamine) 2.4 g/day and 56% of the patients treated with Asacol® HD (mesalamine) 4.8 g/day experienced overall improvement, although the results were not statistically significant.[24] Comparing Asacol® (mesalamine) 2.4 g/day to Asacol® HD (mesalamine) 4.8 g/day in patients with moderately active disease, a greater proportion of patients in the Asacol® HD (mesalamine) group experienced a clinical response, achievement of remission and overall disease improvement.[25] In a study comparing Asacol® HD (mesalamine) and Asacol® (mesalamine) preparations, 70.2 and 65.5% of patients receiving Asacol® HD (mesalamine) and Asacol® (mesalamine), respectively, achieved treatment success after six weeks of therapy; however, a significantly greater proportion of patients receiving Asacol® HD (mesalamine) achieved clinical remission at three weeks. The primary objective of non inferiority for this trial was met.[26] When evaluating Asacol® (mesalamine) administered once daily compared to twice daily, Asacol® (mesalamine) once-daily was found to be non inferior to twice daily dosing, with a similar number of patients in each group maintaining clinical remission at six months (90.5 vs 91.8%, respectively).[27] In one trial, treatment with Lialda® (mesalamine) was found to be non inferior to Asacol® with regard to maintenance of endoscopic remission at six months in patients with UC.[28] The results of clinical trials have not demonstrated statistically significant differences in rates of clinical remission between treatment with balsalazide and sulfasalazine (*P*=0.19) or olsalazine and mesalamine (*P*=0.67).[23,32]

A Cochrane review of the oral 5-ASA derivative preparations for the induction of remission in patients with UC demonstrates that newer 5-ASA derivatives were significantly more effective compared to placebo. There was a nonsignificant trend towards therapeutic benefit over sulfasalazine.[34] A study comparing

Asacol® (mesalamine) 2.4 g/day, 3.6 g/day, Pentasa® (mesalamine) 2.25 g/day, and placebo among adults with moderately active UC demonstrated that the reduction in disease activity index scores was most prominent with Asacol® (mesalamine) 3.6 g/day. This study concluded that Asacol® (mesalamine) 3.6 g/day was more effective compared to Pentasa® (mesalamine) 2.25 g/day. In addition, Asacol® (mesalamine) 2.4 g/day was non inferior to Pentasa® (mesalamine) 2.25 g/day.[30] In a study comparing Apriso® (mesalamine)1.5 g/day administered once daily compared to placebo, a greater proportion of patients with UC (previously in remission) remained in remission at six months following treatment with Apriso® (mesalamine) compared to placebo (78.9 vs 58.3%; *P*<0.001). The number needed to treat analysis concluded that one UC relapse was prevented for every five patients treated with mesalamine.[31]

A meta-analysis that evaluated mesalamine once daily compared to multiple daily dosing regimens found that mesalamine once-daily is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of UC. Moreover, it is even more effective for inducing remission in active UC.[29] Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal UC.[36] In an open-label trial assessing mesalamine 500 mg suppository among pediatric patients with ulcerative proctitis, a significant reduction in mean disease activity index scores was reported at six weeks compared to baseline. Significant differences were observed for stool frequency during the day and night, urgency of defecation, blood in stools, and general well-being disease activity index components) between baseline and three weeks and baseline and six weeks.[37] In a meta-analysis comparing rectal 5-ASA therapy to placebo or other active agents for the treatment of distal disease, rectal 5-ASA therapy was significantly more effective compared to placebo and rectal corticosteroids. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[39] A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat of three. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[35] In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to either topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy appeared to be more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Also, intermittent topical 5-ASA therapy was reported to be significantly more effective compared to oral 5-ASA therapy for preventing relapse of quiescent UC.[38]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oral Route of Administration				
Scherl et al[22] Balsalazide (Giazo®) 6.6 g/day divided BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with mild-to-moderate active ulcerative colitis, baseline MMDAI score of 6 to 10 and who had not received >6.75 g/day balsalazide or >2.4 g/day mesalamine within previous 14 days	N=249 8 weeks	Primary: Proportion of patients that achieved clinical improvement and improvement in the rectal bleeding subscale of the MMDAI at week eight (three point or greater improvement from baseline in total MMDAI score and at least one point improvement in the rectal bleeding subscale of the MMDAI) Secondary: Proportion of patients in clinical remission (score of zero for rectal bleeding and a combined score of two or less for bowel frequency and physician assessment using the MMDAI subscales), proportion of patients who experienced mucosal healing (endoscopy/sigmoid-oscopy score of one or less), proportion of patients with	Primary: In the ITT population the proportion of patients who achieved clinical improvement and an improvement in rectal bleeding was significantly higher with balsalazide treatment compared to placebo (55 vs 40%; *P*=0.02). Similar results were reported in the PP population (58 vs 41%; *P*=0.02). Secondary: A significantly greater proportion of patients treated with balsalazide achieved clinical remission compared to patients treated with placebo (39 vs 23%; *P*=0.01). Significantly more patients treated with balsalazide experienced mucosal healing at eight weeks compared to patients treated with placebo (53 vs 33%; *P*=0.004). A significantly greater proportion of patients receiving balsalazide compared to placebo experienced an improvement in the MMDAI subscale components of rectal bleeding (59 vs 42%; *P*=0.01) and complete resolution (score of zero) of rectal bleeding (48 vs 29%; *P*=0.005). Significantly more patients in the balsalazide treatment group experienced improvement in MMDAI subscale components compared to placebo for physician's assessment (60 vs 36%; *P*=0.0004), bowel frequency (49 vs 37%; *P*=0.08) and complete remission (21 vs 13%; *P*=0.10). A significantly greater proportion of patients treated with balsalazide experienced improvement in MMDAI score compared to the placebo group (67 vs 47%; *P*=0.004). The mean change from baseline to eight weeks in the total MMDAI score was significantly greater with balsalazide compared to placebo (-3.4 vs - 2.3; *P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			improvement (at least one point improvement from baseline in MMDAI subscale of mucosal appearance, bowel frequency, rectal bleeding and physician assessment), proportion of patients achieving complete remission (MMDAI score of one or less) and mean change from baseline in the MMDAI score	
Green et al[23] Balsalazide 6.75 g/day divided TID vs sulfasalazine 3 g/day divided TID Use of topical and/or oral corticosteroids was permitted.	AC, DB, MC, PG, RCT Patients ≥18 years of age with mild to severe active ulcerative colitis (newly diagnosed/ recent relapse) confirmed by sigmoidoscopy and a negative stool culture	N=57 (30 of 57 patients had previous treatment with sulfasalazine) 12 weeks	Primary: Rate of remission Secondary: Withdrawal rate secondary to adverse events	Primary: A greater number of patients in the balsalazide group (75%) achieved remission compared to the sulfasalazine group (59%); however, the difference was not statistically significant (*P*=0.19). Secondary: Fewer patients receiving balsalazide withdrew from the study compared to those in the sulfasalazine group (2 vs 9; *P*=0.041). The most common adverse events were headache, abdominal pain, nausea and dyspepsia. All were reported in both groups.
Hanauer et al[24] (ASCEND I) Delayed-release oral mesalamine 2.4 g/day divided TID (400 mg tablet)	AC, DB, MC, RCT Patients 18 to 75 years of age with confirmed ulcerative colitis (proctitis to colitis) confirmed via	N=301 6 weeks	Primary: Overall improvement in disease (i.e., treatment success) from baseline to six weeks Secondary: The proportion of	Primary: Among the ITT population, the percentage of patients with treatment success, defined as complete remission or response to therapy, at six weeks was not statistically different between the two treatment groups. At six weeks, 51% of the group receiving delayed-release oral mesalamine 2.4 g/day and 56% of the group receiving delayed-release oral mesalamine 4.8 g/day experienced overall improvement (*P*=0.441).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs delayed-release oral mesalamine 4.8 g/day divided TID (800 mg tablet)	endoscopy/ radiography within 24 months, with mild-moderate ulcerative colitis and a PGA score 1 or 2 at baseline		patients who improved at three weeks (from baseline) and the percentage of patients whose clinical assessment scores improved from baseline scores at three and six weeks, improvement in QOL from baseline to three and six weeks, and time to symptom relief (stool frequency, rectal bleeding or both), adverse events and clinical laboratory evaluations	Secondary: At three weeks the percentage of patients with overall improvement was 42 and 39% among the delayed-release oral mesalamine 2.4 and 4.8 g/day treatment groups, respectively (*P*=0.5677). The median time for patients to return to normal stool frequency and for rectal bleeding to resolve was not statistically different between the treatment groups. The median time for both clinical assessments (i.e., rectal bleeding and stool frequency) to resolve and return to normal was shorter in the patients who received delayed-release oral mesalamine 4.8 g/day compared to patients who received delayed-release oral mesalamine 2.4 g/day, corresponding to a time difference of nine days. The time to resolution and return to normal was 15 days for the 4.8 g/day group and 24 days for the 2.4 g/day treatment group (*P*=0.0719). The total IBDQ scores and all QOL subcategory scores improved significantly from baseline to three and six weeks in both treatment groups. The total IBDQ score and all subcategory scores, with the exception of social score, showed a statistically greater improvement among patients who received 4.8 g/day compared to those who received 2.4 g/day. Among patients with moderate disease, the difference in overall improvement was 15%, favoring the 4.8 g/day treatment group (72 vs 57%; 95% CI, 1.16 to 29.6; *P*=0.0384). The total IBDQ scores and all QOL subcategory scores improved significantly from baseline to three and six weeks in both treatment groups. The total IBDQ score and all subcategory scores, with the exception of social score, showed a statistically greater improvement among patients who received 4.8 g/day compared to those who received 2.4 g/day.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Five percent of patients in the 2.4 g/day treatment group discontinued treatment due to an adverse event compared to 3% in the 4.8 g/day group. Serious adverse events occurred in 2 and 1% of the patients treated with 2.4 g/day and 4.8 g/day groups, respectively. No clinically significant changes in laboratory values from baseline were seen in either group, and no significant differences were observed between treatment groups.
Hanauer et al[25] (ASCEND II) Delayed-release oral mesalamine 2.4 g/day divided TID (400 mg tablet) vs delayed-release oral mesalamine 4.8 g/day divided TID (800 mg tablet)	AC, DB, MC, RCT Patients 18 to 75 years of age with confirmed ulcerative colitis via endoscopy/ radiography within 24 months, with moderately active ulcerative colitis (i.e., baseline PGA score of 2)	N=386 6 weeks	Primary: Overall improvement in disease (i.e., treatment success) from baseline to six weeks Secondary: Proportion of patients with overall improvement at three weeks, improvement in clinical assessment subscores at three and six weeks, overall improvement at six weeks in patients with left-sided disease (proctitis, proctosigmoiditis, or left-sided colitis), time to normalization of stool frequency and time to resolution of rectal bleeding (i.e., patient's daily diary), and change from baseline in the UC-DAI	Primary: At six weeks, 59.2% of patients in the 2.4 g/day group and 71.8% of patients in the 4.8 g/day group were classified as having overall improvement; corresponding to a difference in overall improvement rate of 12.5% (95% CI, 0.96 to 24.12; *P*=0.036). In the 2.4 g/day group in which 59.2% of patients were classified as having overall improvement, 41.5% experienced a clinical response to therapy and improved, while 17.7% achieved complete remission. Conversely, in the 4.8 g/day group in which 71.8% of patients were classified as having overall improvement, 51.6% experienced a clinical response to therapy and improved while 20.2% achieved complete remission. Secondary: At three weeks, 51.5% of patients in the 2.4 g/day group were reported as having overall improvement compared to 61.3% of patients in the 4.8 g/day group (*P*=0.117). The rates of improvement for individual clinical assessments (including stool frequency, rectal bleeding, PGA, and endoscopy scores) were greater at three and six weeks in the 4.8 g/day group compared to the 2.4 g/day group (*P*=NS). The rates of overall improvement in patients with left-sided disease (i.e., proctitis, proctosigmoiditis and left-sided colitis) and those with pan-colonic involvement were greater at six weeks in the 4.8 g/day group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to the 2.4 g/day group (*P*=NS). The median times to symptom resolution (stool frequency, rectal bleeding and both) favored the 4.8 g/day group compared to the 2.4 g/day group. The median time for rectal bleeding to resolve was significantly shorter in the 4.8 g/day group compared to the 2.4 g/day group (9 vs 16 days; *P*=0.035). Although the median time for stool frequency to resolve favored the 4.8 g/day group by three days compared to the 2.4 g/day group (10 vs 13 days, respectively), the results were not statistically significant (*P*=0.2883). The treatment group receiving 2.4 g/day had a 43% improvement from baseline (mean change -3.2 from baseline), while the 4.8 g/day treatment group had a 51% improvement from baseline (mean change -3.7 from baseline); the difference between the two treatment groups was not statistically significant (*P*=0.1594).
Sandborn et al[26] (ASCEND III) Mesalamine, delayed-release tablet (Asacol®) 2.4 g daily vs mesalamine, delayed-release tablet (Asacol® HD) 4.8 g daily	AC, DB, DD, MC, NI, RCT Patients 18 to 75 years of age with a diagnosis of moderately active ulcerative colitis that extended proximally beyond 15 cm from the anal verge	N=772 6 weeks	Primary: Treatment success at six weeks Secondary: Clinical remission at three and six weeks; improvement in stool frequency, rectal bleeding, and PFA at three and six weeks; improvement in the sigmoidoscopy with contact friability test, PGA, and UC-DAI at six weeks; and treatment success in patients with left-sided disease at six weeks	Primary: At six weeks, 70.2% (273/389) and 65.5% (251/383) of patients receiving 4.8 and 2.4 g daily of delayed-release mesalamine achieved treatment success (95% CI, -11.2 to 1.9). The primary objective of NI was met and the comparison of 4.8 to 2.4 g/day for superiority was not significant (*P*=0.17). Secondary: A significantly greater proportion of patients who received 4.8 g/day compared to 2.4 g/day achieved clinical remission at three (25 vs 18%; *P*=0.02) and six weeks (43 vs 35%; *P*=0.04). Rates of improvement for individual assessments, including stool frequency, rectal bleeding and PFA were greater at three and six weeks in the 4.8 g/day group, but the differences were not statistically significant (*P* values not reported). The rate of improvement for PGA was greater at six weeks only for those patients receiving 4.8 g/day; however, the difference was not

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				statistically significant. Also at six weeks, 30.2% (105/348) of patients in the 4.8 g/day group achieved improvement in the sigmoidoscopy with contact friability test score, compare with 30.7% (106/345) of those who received 2.4 g/day (*P*=0.88). The mean change from baseline in UC-DAI was statistically significant for both the 4.8 g/day group (-3.3 points) and the 2.4 g/day group (-3.1 points) compared to baseline (*P*<0.001); however, the difference between the two groups was not significant (*P*=0.20). At six weeks, rates of treatment success in patients with left-sided disease were 72.1% (233/323) of patients receiving 4.8 g/day compared to 67.4% (215/319) of patients receiving 2.4 g/day (*P*=0.19).
Sandborn et al[27] (QDIEM trial) Mesalamine delayed-release (Asacol®) 1.6 to 2.4 g/day QD vs mesalamine delayed-release (Asacol®) 1.6 to 2.4 g/day divided BID	AC, MC, NI, RCT, SB Patients ≥18 years of age with ulcerative colitis in clinical remission for ≥3 months on mesalamine (Asacol®) at a stable dose ranging from 1.6 to 2.4 g/day who have a history of at ≥1 flare of ulcerative colitis in the previous 18 months	N=1,023 12 months	Primary: Maintenance of clinical remission at six months in the ITT Secondary: The time to relapse measured from the first dosing date to diagnosis of relapse; maintenance of clinical remission at three and 12 months; patient-defined remission at six and 12 months; MARS assessment at three, six, and 12 months; and patient satisfaction and preference with treatment regimen at six and 12 months	Primary: At six months, 90.5% of patients who received the mesalamine regimen QD had maintained clinical remission compared to 91.8% of those who received the regimen dosed BID (95% CI [BID to QD], -2.3 to 4.9; *P*=0.50); thus establishing that QD dosing is NI to BID dosing. Secondary: There were no significant differences between the two dosing regimens in the rates of clinical remission at three months, which had a treatment difference 0.8 (95% CI, -1.8 to 3.5; *P*=0.54) and 12 months, which had a treatment difference 0.0 (95% CI, -4.6 to 4.7; *P*=0.98). At six months, the time to relapse was similar between the QD and BID dosing regimens with a corresponding HR of 1.17 (95% CI, 0.76 to 1.80; *P* value not reported). At 12 months, the time to relapse was similar between the QD and BID dosing regimens with a corresponding HR of 1.01 (95% CI, 0.71 to 1.42; *P* value not reported). There were no significant differences in patient-defined remission between the two dosing regimens at six months with 83.1 and 86.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients dosed QD and BID, respectively (95% CI [for BID to QD dosing], -1.3 to 8.5). There were also no significant differences at 12 months with 83.4, and 85.4% of patients dosed QD and BID, respectively (95% CI [BID to QD], -3.5 to 7.5). Patients who relapsed had similar MARS questionnaire scores as compared to those who did not relapse. There were slight differences in MARS scores between the QD and BID dosing regimens at three months (*P*=0.04); however the differences were not statistically significant at six or 12 months. At six months, there was no statistically significant difference in patient satisfaction between the QD and BID dosing regimens (*P*=0.08); however, at 12 months, patients were more satisfied with the QD regimen (*P*=0.01).
D'Haens et al[28] Mesalamine multi-matrix release (Lialda®) 2.4 g/day QD vs mesalamine delayed-release (Asacol®) 1.6 g/day divided BID	AC, DB, MC, RCT Patients ≥18 years of age with ulcerative colitis that was in remission for ≥30 days on a stable dose of mesalamine (≤2.4 g/day) or the equivalent dose of sulfasalazine (≤6.2 g/day), with an endoscopy score of ≤1, combined symptom score ≤1.	N=826 6 months	Primary: Endoscopic remission at six months in PP population (modified UC-DAI endoscopy subscore of one point or less) Secondary: Maintenance of mucosal healing with no or mild symptoms (combined modified UC-DAI-defined stool frequency and rectal bleeding subscores of one or less) at six months, time to relapse (withdrawal due to lack of efficacy), modified UC-DAI score	Primary: In the PP population, 83.7% (287/343) of patients treated with Lialda® maintained endoscopic remission compared to 81.5% (274/336) of patients treated with Asacol® (difference, 2.2%; 95% CI, -3.9 to 8.1). Similar results were reported for the ITT population with regard to endoscopic remission (difference, 0.9%; 95% CI, -5.0 to 6.9). Secondary: The proportion of patients in the PP population who maintained endoscopic remission with no or mild symptoms at six months was 79.0% (271/343) for patients treated with Lialda® compared to 75.6% (254/336) of patients treated with Asacol® (difference, 3.4%; 95% CI, -3.2 to 10.0). In the ITT population, 72.8% (302/415) of patients receiving Lialda® maintained endoscopic remission with no or mild symptoms compared to 70.8% (291/411) of patients treated with Asacol® (difference, 2.0%; 95% CI, -4.4 to 8.3). There was no statistically significant difference in the time to relapse (withdrawal due to relapse) between patients treated with Lialda® compared to Asacol® in the PP population (12.8 vs 14.6%, respectively;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	All patients had experienced ≥1 acute flare of ulcerative colitis in the past 12 months, with ≥2 acute flares in their medical history		and its components (rectal bleeding, stool frequency, endoscopy, and PGA scores) and safety	*P*=0.5116). Similar results were reported in the ITT population (12.3 vs 13.9%, respectively; *P*=0.5455). There were small mean increases in the modified UC-DAI score from baseline to six months for patients in both PP treatment groups. Overall, 37.1% of patients treated with Lialda® experienced treatment-emergent adverse events compared to 36.0% of patients treated with Asacol®. Six patients treated with Lialda® experienced seven serious adverse events; with three patients receiving Asacol® reported four serious adverse events. None were considered to be related to the study drug. There were no significant changes from baseline in mean serum creatinine the treatment groups.
Tong et al[29] Mesalamine (any dose) QD or multiple daily dosing for the management of ulcerative colitis Note: daily doses of QD regimens had to be equal to the daily doses of the BID regimens.	MA Patients with active or quiescent ulcerative colitis treated with any dose of mesalamine for ≥2 weeks for the induction of remission trials in active ulcerative colitis, and ≥6 months in prevention of relapse trials in quiescent UC	N=3,410 10 trials (2 trials were for inducing remission in active ulcerative colitis and 8 for preventing the relapse of quiescent ulcerative colitis)	Primary: Proportion of patients with a failure to achieve remission in active ulcerative colitis, and to prevent a relapse of disease in quiescent ulcerative colitis Secondary: Assessment of adverse events during treatment, discontinuations due to adverse events and compliance	Primary *Preventing relapse in quiescent disease:* Among the ITT group, 26.3% of patients with QD dosing relapsed compared to 26.5% of patients with multiple-dosing (RR, 1.00; 95% CI, 0.89 to 1.12) There was no significant increased risk of relapse within a year in quiescent ulcerative colitis patients (RR, 0.97; 95% CI, 0.74 to 1.27). Subgroup analysis of the eight studies using different formulations revealed there was no significant difference for relapse rates between QD and multiple-dosing regimens with mesalamine (Asacol®) (RR, 0.93; 95% CI, 0.72 to 1.19) and 5-ASA-multi-matrix mesalamine (Lialda®) (RR, 1.09; 95% CI, 0.90 to1.32). Patients with ulcerative colitis given Pentasa® 2 g QD had better remission rates compared to those given oral mesalamine 1 g BID in one trial; however, another study failed to demonstrate the NI of 1.5 g QD Salofalk® (Germany) compared to a standard 0.5 g TID regimen in maintaining remission. *Inducing remission in active disease:*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Among the ITT analysis, remission of ulcerative colitis was not achieved in 29.8% of patients that received QD dosing compared to 37.8% of patients that received a multiple-dosing regimen. The RR of failure to achieve remission with QD and multiple-dosing regimens was 0.80 (95% CI, 0.64 to 0.99; *P*=0.259). Secondary: No statistically significant differences were observed in the incidence of total adverse events (RR of any adverse event, 1.06; 95% CI, 0.93 to 1.20), serious adverse events (RR, 1.48; 95% CI, 0.92 to 2.41), and discontinuations due to adverse events (RR, 1.00; 95% CI, 0.99 to 1.02) with QD vs multiple-dosing regimens among the four trials assessing the prevention of relapse in quiescent disease that reported adverse event data. There was no statistically significant difference detected in the chance of experiencing any adverse event with QD vs multiple-dosing regimens (RR, 0.99; 95% CI, 0.89 to 1.10), serious adverse events (RR, 1.00; 95% CI, 0.98 to 1.02), and discontinuations due to adverse events (RR, 1.00; 95% CI, 0.98 to 1.03) among the two trials on inducing remission that reported adverse event data. The compliance rate for the QD group was 77.7% compared to 76.0% for the multiple-dosing group. Compliance with QD was slightly higher than the multiple-dosing group; however the difference was not significant (RR, 0.92; 95% CI, 0.82 to 1.03; *P*=0.502).
Ito et al[30] Mesalamine 2.4 g/day (Asacol®) vs mesalamine 3.6 g/day (Asacol®)	AC, DB, MC, NI, PC, RCT Outpatients 16 to 64 years of age with mild to moderately active ulcerative colitis defined by a DAI	N=229 8 weeks	Primary: Decrease in the UC-DAI Secondary: The proportion of patients achieving “remission” and “efficacy”	Primary: The decrease in UC-DAI was most pronounced in the mesalamine 3.6 g/day group. The decrease in UC-DAI was greater by 1.6 in the mesalamine 3.6 g/day group compared to the mesalamine 2.25 g/day group, demonstrating the superiority of mesalamine 3.6 g/day over mesalamine 2.25 g/day (95% CI, 0.6 to 2.6; *P*=0.003). The difference in UC-DAI between mesalamine 2.4 g/day and mesalamine 2.25 g/day was 0.2,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mesalamine 2.25 g/day (Pentasa®) vs placebo	of 3 to 8 and a bloody stool score >1			demonstrating the NI of mesalamine 2.4 g/day to mesalamine 2.25 g/day (95% CI, -0.8 to 1.2). The difference in UC-DAI between the mesalamine 3.6 g/day group compared to the placebo group was 2.7 (95% CI, 1.4 to 3.9) and between mesalamine 2.4 g/day and placebo was 1.2 (95% CI, 0.0 to 2.5). The difference in UC-DAI between mesalamine 2.25 g/day and placebo was 1.1 (95% CI, -0.1 to 2.3). Secondary: The proportion of patients who experienced a remission (i.e., UC-DAI score of two or less and a bloody stool score of zero at the final assessment) was 30.3% (95% CI, 19.6 to 42.8) in the mesalamine 2.4 g/day group, 45.3% (95% CI, 32.9 to 58.2) in the mesalamine 3.6 g/day group, 28.6% (95% CI, 17.9 to 41.3) in the mesalamine 2.25 g/day group, and 9.4% (95% CI, 2.0 to 25.0) in the placebo group. Efficacy (i.e., decrease in UC-DAI by two points or more) was archived by 45.5% (95% CI, 33.2 to 58.1) in the mesalamine 2.4 g/day group, 64.1% (95% CI, 51.1 to 75.6) in the mesalamine 3.6 g/day group, 49.2% (95% CI, 36.4 to 62.1) in the mesalamine 2.25 g/day group, and 28.1% (95% CI, 13.8 to 46.7) in the placebo group.
Lichtenstein et al[31] Mesalamine granules 1.5 g capsules QD (Apriso® dosed as four 0.375 g capsules) vs placebo	DB, PC, RCT Patients ≥18 years of age with ulcerative colitis who were in remission for ≥1 month (but not > 12 months), had a history ≥1 flare with symptoms	N=305 6 months (treatment phase)	Primary: The percentage of patients who remained relapse-free at six months (relapse or failure defined as a rectal bleeding score at least one and a mucosal appearance score of at least two on the Sutherland DAI, a	Primary: The proportion of patients who were relapse-free at month-six was significantly higher in the mesalamine group compared to the placebo group (78.9 vs 58.3%, respectively; *P*<0.001). The proportion of patients who were relapse-free at month-six was significantly higher in the mesalamine group compared to the placebo group (78.9 vs 58.3%, respectively; *P*<0.001). For the probability of remaining relapse-free, the NNT analysis revealed that one ulcerative colitis relapse was prevented for every five patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	requiring intervention within the past year without steroids or immune-suppressants within the previous 30 days		ulcerative colitis flare, or initiation of medication previously used to treat a ulcerative colitis flare) Secondary: The percentages of patients with each level of change from baseline in rectal bleeding score, mucosal appearance score, physician's rating of disease activity and stool frequency on the Sutherland DAI at one, three, and six months; mean change from baseline in the Sutherland DAI at six months; the percentage of patients classified as treatment successes (defined as maintaining the Sutherland DAI total score two or less with no individual component greater than one and rectal bleeding score of zero at six months; and relapse-free duration (defined as the number of days between the start of study drug and the date of first relapse or study withdrawal plus	treated with mesalamine. Secondary: Statistically significant differences supporting mesalamine over placebo were seen for the proportions of patients at each level of change from baseline in the Sutherland DAI scores for rectal bleeding (*P*=0.008), physician's rating of disease activity (*P*=0.005), stool frequency (*P*=0.005); the proportion of patients classified as treatment successes (*P*=0.003); mean change from baseline in the Sutherland DAI total score (*P*=0.025); and probability of remaining relapse-free over six months (*P*<0.001). Although the other secondary endpoint measure (the proportion of patients at each level of change from baseline in the Sutherland DAI for mucosal appearance) favored mesalamine over placebo, the results were not statistically significant (*P*=0.098). Headache was the most commonly reported event (other than worsening ulcerative colitis), occurring in a higher percentage of patients treated with mesalamine compared to patients treated with placebo (11 vs 7%, respectively). Treatment-emergent events causing discontinuation (other than worsening ulcerative colitis) occurred in 4.3% of mesalamine-treated patients and 2.1% of placebo-treated patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			one day).	
Kruis et al[32] Olsalazine 1 g TID vs mesalamine 1 g TID The daily dose of olsalazine was increased gradually from 500 mg to 3 g during the first week.	DB, DD, MC, RCT Patients 18 to 75 years of age with mild to moderate active ulcerative colitis extending >15 cm and ≥1 attack in the last 5 years, a negative stool culture	N=168 12 weeks	Primary: Endoscopic remission (a score of one or less on a five point scale) Secondary: Clinical activity index score (sum of total scores assessing number of stools/bloody stools per week, frequency of abdominal pain/cramps per week, temperature secondary to colitis, presence of extra-intestinal manifestations, laboratory findings) on a scale of one (remission) to six (severe active disease), global assessment of patient response on a scale of zero (good) to three (very poor)	Primary: Remission was achieved in 52.2% of patients receiving olsalazine compared to 48.8% of the mesalamine group, a difference that was not statistically significant (*P*=0.67). Secondary: The mean change in clinical activity score in the olsalazine group was a reduction of 2.92±3.49, whereas a reduction of 3.18±3.11 was reported in the mesalamine arm. The difference between the groups did not reach statistical significance (*P*=0.31). The proportion of patients achieving clinical remission was similar among groups (45.4% of olsalazine patients compared to 46.2% of mesalamine patients; *P* value not reported). The differences between groups regarding the global assessment of symptoms were not statistically significant. No significant difference in adverse events was found between groups.
Feagan et al[33] 5-ASA vs placebo or	MA Patients with mild to moderate ulcerative colitis in remission	N=8,127 ≥6 months	Primary: Failure to maintain clinical or endoscopic remission Secondary: Proportion of patients who failed to adhere with their medication	Primary: There was a lower risk of failure to maintain clinical or endoscopic remission with 5-ASA compared to placebo (RR, 0.69; 95% CI, 0.62 to 0.77; *P*<0.00001). Compared to placebo, 5-ASA was associated with a lower risk of treatment failure when stratified by doses up to 1.9 g/day (RR, 0.65; 95% CI, 0.56 to 0.76; *P*<0.00001) and doses ≥2 g/day (RR, 0.73; 95% CI, 60 to 0.89; *P*=0.002). There was a greater risk of failure to maintain clinical or endoscopic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5-ASA vs sulfasalazine or 5-ASA vs 5-ASA			regimen, who experienced at least one adverse event, who withdrew due to adverse events and patients excluded or withdrawn after entry	remission with 5-ASA compared to sulfasalazine (RR, 1.14; 95% CI, 1.03 to 1.27; *P*=0.01). No statistically significant differences between the treatments were reported when the analysis was limited to studies lasting 12 months (RR, 1.10; 95% CI, 0.98 to 1.23). There was no statistically significant differences between once-daily dosing and conventional dosing of 5-ASA products with regard to relapse rates at six months (RR, 1.02; 95% CI, 0.85 to 1.23) or 12 months (RR, 0.92; 95% CI, 0.83 to 1.03). There were no statistically significant differences in relapses between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.01; 95% CI, 0.80 to 1.28; *P*=0.95). Secondary: There was no statistically significant difference in the incidence of adverse events between patients treated with 5-ASA and placebo (RR, 0.98; 95% CI, 0.69 to 1.39; *P*=0.91). There was no statistically significant difference in the risk of developing at least one adverse event between patients receiving 5-ASA and sulfasalazine (RR, 1.07; 95% CI, 0.82 to 1.40). Moreover, there was no statistically significant difference in the proportion of patients who reported at least one adverse events between patients receiving daily dosing or conventional dosing (RR, 1.01; 95% CI, 0.92 to 1.11). There was no statistically significant difference in the incidence of adverse events between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 0.94; 95% CI, 0.83 to 1.07). There was no statistically significant difference in withdrawal due to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse events between patients treated with 5-ASA and placebo (RR, 1.34; 95% CI, 0.78 to 2.30). Moreover, there was no statistically significant difference in withdrawals due to adverse events between the 5-ASA and sulfasalazine treatment groups (RR, 1.27; 95% CI, 0.87 to 1.87). There was no statistically significant difference in withdrawal due to adverse events between patients receiving daily dosing or conventional dosing (RR, 1.26; 95% CI, 0.76 to 2.10). There was no statistically significant difference in withdrawal due to adverse events between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.25; 95% CI, 0.56 to 2.78). There was no statistically significant difference in the proportion of patients withdrawn or excluded after entry between those receiving 5-ASA and placebo (RR, 1.13; 95% CI, 0.88 to 1.44). Significantly more patients treated with 5-ASA were excluded or withdrawn after entry compared patients treated with sulfasalazine (RR, 1.30; 95%, CI, 1.04 to 1.63). There was no statistically significant difference in exclusions or withdrawals after entry between patients receiving once-daily or conventional dosing regimens (RR, 0.99; 95% CI, 0.85 to 1.15). There was no statistically significant difference in exclusions or withdrawals after entry between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.23; 95% CI, 0.90 to 1.70).
Feagan et al[34] 5-ASA	MA Patients ≥18 years	N=7,776 Duration not	Primary: Proportion of patients who failed to enter	Primary: There was a significantly lower risk of failing to achieve remission with 5-ASA compared to placebo (RR, 0.86; 95% CI, 0.81 to 0.91; *P*<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or 5-ASA vs sulfasalazine or 5-ASA vs 5-ASA	of age with active mild to moderate ulcerative colitis	reported	complete global or clinical remission Secondary: Proportion of patients who failed to improve clinically, who failed to enter endoscopic remission, who failed to improve endoscopically, who failed to adhere to medication regimen, who experienced at least one adverse event, who withdrew due to adverse events and who were excluded or withdrawn after entry	There was no difference in remission rates when stratified by once-daily or conventional dosing (RR, 0.95; 95% CI, 0.82 to 1.10; *P*=0.49). There was no statistically significant difference in failure to enter global or clinical remission between various formulations of 5-ASA (RR, 0.94; 95% CI, 0.86 to 1.02; *P*=0.11). There was no statistically significant difference in the failure to induce complete global or clinical remission between patients treated with 5-ASA and sulfasalazine (RR, 0.90; 95% CI, 0.77 to 1.04; *P*=0.15). Furthermore, there was no difference between patients who received once daily dosing or conventional dosing with regard to failure to induce global or clinical improvement (RR, 0.87; 95% CI, 0.68 to 1.10). Secondary: Significantly fewer patients treated with 5-ASA failed to improve clinically compared patients treated with placebo (RR, 0.68; 95% CI, 0.60 to 0.76; *P*<0.00001). There was no statistically significant difference in the risk of inducing clinical or global improvement with 5-ASA compared to sulfasalazine (RR, 0.88; 95% CI, 0.77 to 1.01; *P*=0.07). There was no statistically significant difference in failure to improve clinically between the various formulations of 5-ASA (RR, 0.89; 95% CI, 0.77 to 1.01). Treatment with 5-ASA was associated with a significantly lower risk of failure to enter endoscopic remission compared to treatment with placebo (RR, 0.77; 95% CI, 0.67 to 0.87; *P*=0.0003). There was no difference between 5-ASA and sulfasalazine with regard to the failure to induce endoscopic improvement (RR, 0.82; 95% CI, 0.65 to 1.02; *P*=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in adverse events between patients treated with 5-ASA and placebo (RR, 0.97; 95% CI, 0.85 to 1.11; *P*=0.65). Patients treated with sulfasalazine were more likely to experience an adverse event compared to patients treated with 5-ASA (RR, 0.48; 95% CI, 0.37 to 0.63; *P*<0.00001). There was no statistically significant difference in the incidence of adverse events between once-daily and conventionally dosed patients (RR, 0.88; 95% CI, 0.70 to 1.10; *P*=0.25). There was no difference in the incidence of adverse events between the various formulations of 5-ASA (RR, 1.01; 95%CI, 0.92 to 1.12; *P*=0.81). There was no statistically significant difference in the risk of withdrawal due to adverse events between patients treated with 5-ASA and placebo (RR, 0.88; 95% CI, 0.62 to 1.24; *P*=0.39). A significantly higher proportion of patients treated with sulfasalazine withdrew due to adverse events compared to patients treated with 5-ASA (RR, 0.40; 95% CI, 0.24 to 0.69; *P*=0.0009). There was no statistically significant difference in the proportion of patients withdrawn due to adverse events between once-daily and conventionally-dosed patients (RR, 0.37; 95% CI, 0.10 to 1.38; *P*=0.14). Similarly, there was no difference in withdrawal due to adverse events between various formulations of 5-ASA (RR, 0.94: 95% CI, 0.57 to 1.54; *P*=0.79). Significantly fewer 5-ASA patients were withdrawn or excluded after entry compared to placebo-treated patients (RR, 0.62; 95% CI, 0.52 to 0.74; *P*<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients excluded or withdrawn after entry was significantly higher with sulfasalazine compared to treatment with 5-ASA (RR, 0.76; 95% CI, 0.58 to 0.99; *P*=0.04). There was no significant difference in the proportion of patients excluded or withdrawn after entry between once-daily and conventionally-dosed patients (RR, 0.96; 95% CI, 0.67 to 1.38; *P*=0.85). There were no differences in exclusions or withdrawals after entry between various formulations of 5-ASA (RR, 0.99: 95% CI, 0.80 to 1.22; *P*=0.91).
Ford et al[35] Topical 5-ASA therapies or a combination of topical and oral 5-ASA agents with oral 5-ASA with a minimum duration of therapy of 14 days for trials assessing the induction of remission of active ulcerative colitis and 6 months for trials assessing the prevention of relapse of quiescent ulcerative colitis. Note: any dose of 5-ASA products was permitted.	MA Adults with active or quiescent ulcerative colitis	N=721 12 trials (3 weeks to 24 months treatment duration)	Primary: The efficacy of oral compared to topical 5-ASAs, and oral 5-ASAs compared to combined oral and topical 5-ASAs in terms of failure to achieve remission in active ulcerative colitis, and prevention of relapse of disease activity in quiescent ulcerative colitis Secondary: Mean time to remission, and adverse events occurring as a result of therapy	Primary: A total of 49.5% of patients who received topical 5-ASA therapy failed to achieve remission compared to 58.7% of patients assigned to oral 5-ASA therapy. The RR of failure to achieve remission with topical 5-ASAs vs oral 5-ASAs in active ulcerative colitis was 0.82 (95% CI, 0.52 to 1.28) [four trials]. When the one study that only recruited patients with proctitis was excluded from the analysis, the RR of remission with topical vs oral 5-ASAs increased to 1.04 (95% CI, 0.79 to 1.37). The mean time to remission was 24.8 days in the topical 5-ASA arm and 25.5 days for oral 5-ASAs in the one trial reporting this outcome. Remission of ulcerative colitis was not achieved in 62 (37.3%) of patients who received combined therapy compared to 55.1% of patients who received oral 5-ASA therapy alone. The RR of failure to achieve remission with combined 5-ASA therapy vs oral 5-ASA therapy in active ulcerative colitis was 0.65 (95% CI, 0.47 to 0.91). The NNT with combined 5-ASA therapy to prevent one patient failing to achieve remission was 5 (95% CI, 3 to 13). Two trials reported mean times to remission of which one trial recorded a mean time to remission of 11.9 days in the combined 5-ASA group vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				25.5 days for oral 5-ASA therapy (*P*=0.002), while the second trial reported the mean time to remission as 20.2 days with combination therapy and 22.9 days with oral 5-ASA therapy (*P*=0.29). Relapse of disease occurred in 37.5% of patients treated with topical therapy compared to 61.5% of patients treated with oral 5-ASA therapy. The RR of relapse of disease activity with topical 5-ASA therapy vs oral therapy in quiescent ulcerative colitis was 0.64 (95% CI, 0.43 to 0.95). The NNT with intermittent topical 5-ASA therapy to prevent one ulcerative colitis relapse was four (95% CI, 2 to 14). A total of 42.6% relapses occurred in patients receiving combined therapy compared to 73.5% among patients receiving oral 5-ASA therapy. The RR of relapse with combined compared to oral 5-ASA therapy was 0.48 (95% CI, 0.17 to 1.38). Secondary: There were 22 (21.0%) of 105 topical 5-ASA patients who experienced any adverse event, compared to 36 (33.0%) of 109 oral 5-ASA patients (RR, 0.61; 95% CI, 0.24 to 1.52). A total of 22.3% of patients receiving combined oral and topical 5-ASA therapy reported at least one adverse event compared to 26.9% of patients receiving oral 5-ASA therapy (RR with combined 5-ASA therapy vs oral=0.77; 95% CI, 0.55 to 1.09). Two of the three trials reported no patients in either arm experiencing any adverse events. The third trial no patients among those treated with topical 5-ASA therapy reported adverse events leading to withdrawal compared to two patients who received oral sulfasalazine. Total adverse events data were reported in both trials; however, no patients in either trial were reported to have experienced any adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Topical Route of Administration				
Kam et al[36] Mesalamine enema 4 g QD in the evening vs sulfasalazine 1 g QID	DB, DD, MC, PG Patients with active mild to moderate distal ulcerative colitis	N=37 6 weeks	Primary: Clinical efficacy and safety Secondary: Not reported	Primary: A physician-rated clinical global improvement score of either “very much improved” or “much improved” was observed in 94% of mesalamine patients compared to 77% of those receiving sulfasalazine (*P* value not reported). Headache and nausea were the most frequently reported adverse events. A significantly greater number of patients receiving sulfasalazine experienced adverse events compared to mesalamine (83 vs 42%; *P*=0.02). Secondary: Not reported
Heyman et al[37] Mesalamine 500 mg suppository rectally QD at bedtime	MC, NR, OL, SG Pediatric patients 5 to 17 years of age, with ulcerative proctitis confirmed by flexible sigmoidoscopy or colonoscopy and biopsy performed within 7 days of the baseline visit	N=49 6 weeks	Primary: UC-DAI derived from a composite score of stool frequency, urgency of defecation, rectal bleeding and general well-being Secondary: Change from baseline in UC-DAI (to three and six weeks); the change in the total UC-DAI from baseline to three weeks and from three to six weeks; remission rate at three and six weeks and responder rate at three and six weeks	Primary: Significant reductions from baseline were observed in UC-DAI at three (1.6±2.0; P<0.0001) and six weeks (1.5±1.9; *P*<0.0001). At six weeks the mean UC-DAI had decreased by -4.0±2.1 (*P*<0.0001). Secondary: No differences were observed in the change in UC-DAI between three and six weeks. Significant differences were observed for all individual UC-DAI components (stool frequency during the day and night, urgency of defecation, blood in stools and general well-being) between baseline and three and six weeks; however, no statistical differences were observed in individual UC-DAI components between three and six weeks. Response was achieved in 93.3% of patients at three weeks and 91.7% of patients at six weeks. Similarly, a total of 82.2% of patients met the criteria for remission at three weeks, and 81.3% at six weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ford et al[38] Mesalamine topical (sulfasalazine, mesalamine, balsalazide, olsalazine) vs placebo	MA Adults with quiescent ulcerative colitis with ≥24 weeks therapy duration that assessed relapse of disease activity at the last time point in the trial	N=555 7 trials (6 to 24 months duration)	Primary: Prevention of relapse of disease activity in quiescent ulcerative colitis Secondary: Adverse events occurring as a result of therapy	Primary: The RR of relapse of disease activity with topical mesalamine compared to placebo in quiescent ulcerative colitis was 0.60 (95% CI, 0.49 to 0.73). The NNT with topical mesalamine to prevent one patient experiencing a relapse of disease activity was three (95% CI, 2 to 5). Two trials reported data concerning mean time to relapse in both arms. In one trial, the mean time to relapse was 239 days in those treated with topical mesalamine compared to 166 days among those receiving placebo (*P*=0.07). In the second trial, the mean time to relapse was 453 days for mesalamine treated patients compared to 158 days for placebo (*P*=0.001). Secondary: Overall, 10.1% of patients receiving topical mesalamine reported at least one adverse event compared to 10.6% of patients receiving placebo. The RR of an adverse event with topical mesalamine compared to placebo was 1.01 (95% CI, 0.59 to 1.72). There were 7.8% of patients assigned to topical mesalamine who experienced anal canal pain upon enema or suppository insertion compared to 9.3% of patients who received placebo (RR, 0.87; 95% CI, 0.44 to 1.72).
Marshall et al[39] Rectal 5-ASA vs placebo vs another active drug in the treatment of distal ulcerative colitis (e.g., rectal corticosteroids, oral	MA Patients ≥12 years of age with a distal disease margin <60 cm from the anal verge or distal to the splenic flexure	N=38 trials 2 to 8 weeks in duration	Primary: Symptomatic improvement Secondary: Symptomatic remission, histologic improvement or remission, endoscopic improvement or remission and change in DAI	Primary and Secondary: Rectal 5-ASA was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission, with a pooled OR for symptomatic improvement of 8.87 (eight trials; 95%CI, 5.30 to 14.83; *P*<0.00001), pooled OR for endoscopic improvement of 11.18 (five trials; 95% CI, 5.99 to 20.88; *P*<0.00001), pooled OR for histologic improvement of 7.69 (six trials; 95% CI, 3.26 to 18.12; *P*<0.00001), pooled OR for symptomatic remission of 8.30 (eight trials; 95% CI, 4.28 to 16.12; *P*<0.00001), pooled OR for endoscopic remission of 5.31 (seven trials; 95% CI, 3.15 to 8.92; *P*<0.00001), and pooled OR for histologic remission of 6.28 (five trials; 95% CI, 2.74 to 14.40; *P*<0.0001). Rectal 5-ASA was superior to rectal corticosteroids for inducing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5-ASA products)				symptomatic improvement and remission with a pooled OR of 1.56 (six trials; 95% CI, 1.15 to 2.11; *P*=0.004) and 1.65 (six trials; 95% CI, 1.11 to 2.45; *P*=0.01), respectively. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement with a pooled OR of 2.25; 95% CI, 0.53 to 19.54; *P*=0.27). Neither total daily dose nor 5-ASA formulation affected treatment response.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, ITT=intent-to-treat, MA=meta-analysis, MC=multicenter, NI=non-inferiority, NNT=number needed to treat, NR=non-randomized, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel-group, PP=per-protocol, RCT=randomized controlled trial, SB=single-blinded, SG=single group, RR=relative risk
Other abbreviations: 5-ASA=5-aminosalicylic acid, DAI=disease activity index, IBDQ=irritable bowel disease questionnaire, MARS=medication adherence report scale, MMDAI=modified Mayo disease activity index, PFA=patient's functional assessment, PGA=physician's global assessment, QOL=quality of life. UC-DAI=ulcerative colitis disease activity index

Special Populations

Table 5. Special Populations[5-18]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Balsalazide	No dosage adjustment required in the elderly; use with caution. Approved for use in children five to 17 years of age (Colazal®).	Use with caution in patients with a history of renal disease.	No dosage adjustment required.	B	Unknown; use with caution.
Mesalamine (oral)	No dosage adjustment required in the elderly population; use with caution. Safety and efficacy in pediatrics have not been established.	No dosage adjustment required; use with caution and monitor routinely.	No dosage adjustment required; use with caution.	B (Apriso®, Delzicol®, Lialda®, Pentasa®) C (Asacol®, Asacol® HD)	Use with caution; mesalamine and its metabolite have been detected in breast milk.
Mesalamine (rectal)	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatrics have not been established.	No dosage adjustment required; use with caution.	No dosage adjustment required; use with caution.	B	Unknown; use with caution.
Olsalazine	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatrics have not been established.	Patients with impaired renal function should be monitored closely.	Patients with impaired hepatic function should be monitored closely.	C	Small amounts (% not reported); unless the benefit outweighs the risks, do not use in nursing women.
Sulfasalazine	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatric patients <2 years have not been established.	Use with caution in patients with impaired renal function.	Use with caution in patients with impaired renal function.	B	Yes; use caution.*

***** Insignificant amounts of uncleaved sulfasalazine detected in breast milk; sulfapyridine levels are 30 to 60% of those in the maternal serum.

Adverse Drug Events

Table 6. Adverse Drug Events[5-18]

Adverse Event	Balsalazide	Mesalamine*	Olsalazine	Sulfasalazine†
Central Nervous System				
Depression	-	-	1.5	-

Adverse Event	Balsalazide	Mesalamine*	Olsalazine	Sulfasalazine†
Dizziness	-	8 (oral), 1.8 to 3.0 (rectal)	1	-
Headache	14 to 15	2.2 to 35.0 (oral), 6.5 (rectal)	5	✔
Insomnia	2	2 (oral)	-	-
Tinnitus	-	<3 (oral)	-	-
Vertigo	-	<3 (oral)	1	-
Gastrointestinal				
Abdominal pain	6 to 17	1.1 to 18.0 (oral), 8.1 (rectal)	10.1	-
Anorexia	2	1.1 (oral)	1.3	✔
Bloating	-	1.5 (rectal)	1.5	-
Colitis (ulcerative)	6	0.4 to 3.0 (oral), 1.2 (rectal)	-	-
Constipation	1	5 (oral), 1 (rectal)	-	-
Cramps	1	-	10.1	-
Diarrhea	5 to 11	1.7 to 8.0 (oral), 2.1 (rectal)	11.1	-
Dyspepsia	2	1.7 to 6.0 (oral)	4	-
Flatulence	2	1.2 to 4.0 (oral), 6.1 (rectal)	-	-
Gastric distress	-	-	-	✔
Hemorrhoids	-	1.4 (rectal)	-	-
Nausea	<9	1.1 to 13.0 (oral), 5.8 (rectal)	5	✔
Rectal bleeding	-	<3 (oral)	-	-
Rectal pain	-	1.2 to 1.8 (rectal)	-	-
Rectal urgency	-	0.2 (oral)	-	-
Stomatitis	<6	-	1	-
Vomiting	3 to 17	1.1 to 5.0 (oral)	1	✔
Laboratory Abnormalities				
Decreased hematocrit/hemoglobin	-	<3 (oral)	-	✔
Increased triglycerides	-	<3 (oral)	-	-
Transaminases increased	-	<3 (oral)	-	-
Musculoskeletal				
Arthralgia/joint pain	4	<3 to 5 (oral), 2.1 (rectal)	4	-
Arthritis	-	2 (oral)	-	-
Back pain	-	7.0 (oral), 1.4 (rectal)	-	-
Myalgia	1	3 (oral)	-	-
Pain	-	<3 to 14 (oral)	-	-
Pain upon insertion (enema tip)	-	1.4 (rectal)	-	-
Pharyngolaryngeal pain	<6	-	-	-
Respiratory				
Cough	<6	0.3 to 2.0 (oral)	-	-
Dyspnea	-	<3 (oral)	-	-
Nasopharyngitis	3 to 9	2.5 to 4.0 (oral)	-	-
Pharyngitis	2	11 (oral)	-	-
Rhinitis	2	5 (oral)	-	-
Sinusitis	-	3 (oral)	-	-
Upper respiratory tract infection	-	-	1.5	-
Other				
Acne	-	0.2 to 2.0 (oral), 1.2 (rectal)	-	-
Alopecia	-	<3 (oral)	-	-
Asthenia	-	7 (oral)	-	-
Chest pain	-	3 (oral)	-	-

Adverse Event	Balsalazide	Mesalamine*	Olsalazine	Sulfasalazine†
Chills	-	3 (oral)	-	-
Conjunctivitis	-	2 (oral)	-	-
Creatinine clearance, decreased	-	<3 (oral)	-	-
Cyanosis	-	-	-	✔
Dry mouth	1	-	-	-
Dysmenorrhea	<6	3 (oral)	-	-
Eructation	-	16 (oral)	-	-
Fatigue	2	<3.0 (oral), 3.4 (rectal)	1.8	-
Fever	2 to 11	0.7 to 6.0 (oral), 1.2 to 3.2 (rectal)	-	✔
Flu-like disorder	1	3 (oral)	-	-
Hematochezia	0 to 9	-	-	-
Hematuria	-	<3 (oral)	-	-
Heinz body anemia	-	-	-	✔
Hepatitis, cholestatic	-	<3 (oral)	-	-
Hypertonia	-	5 (oral)	-	-
Influenza	3 to 6	1 to 4 (oral), 5.3 (rectal)	-	-
Itching	-	0.6 to 3.0 (oral), 1.2 (rectal)	1.3	✔
Malaise	-	2 (oral)	-	-
Melena	-	0.9 (oral)	-	-
Oligospermia (reversible)	-	-	-	✔
Peripheral edema	-	3 (oral)	-	-
Rash	-	1.3 to 6.0 (oral), 1.2 to 2.8 (rectal)	2.3	✔
Sore throat/cold	-	2.3 (rectal)	-	-
Sweating	-	3 (oral)	-	-
Urinary tract infection	1	-	-	-
Urticaria	-	-	-	✔

✔ Percent not specified.
- Event not reported.
* Adverse events for Rowasa® and sfRowasa® (mesalamine) are identical in the prescribing information; the trials were conducted with Rowasa® (mesalamine).
† Reports of adverse events are consistent within the prescribing information of Azulfidine® and Azulfidine® EN (sulfasalazine).

Contraindications

Table 7. Contraindications[5-18]

Contraindications	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Hypersensitivity to salicylates (including parent drug, metabolites, or excipients)*†	✔	✔	✔	✔
Hypersensitivity to sulfonamides	-	-	-	✔
Intestinal or urinary obstruction	-	-	-	✔
Porphyria	-	-	-	✔

*Hypersensitivity to sulfasalazine: mesalamine enemas (Canasa®) have been used without allergic reactions; exercise caution with use and discontinue at first signs of hypersensitivity.
†Rowasa® contains potassium metabisulfite, a sulfite that may cause hypersensitivity; the risk in the general population is unknown but anticipated as low.

Warnings/Precautions

Table 8. Warnings and Precautions[5-18]

Warnings/Precautions	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Acute intolerance syndrome (cramping, acute abdominal pain, bloody diarrhea, fever, headache, and rash); discontinue therapy immediately	-	✔ (Apriso®, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®, sfRowasa®)	-	-
Asthma (severe allergy & bronchial asthma); use with caution	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Blood dyscrasias (e.g., aplastic anemia, agranulocytosis, etc.); monitor complete blood count and urinalysis routinely	-	✔ (Rowasa®)	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Crystalluria and stone formation; maintain adequate fluid intake	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Delayed drug release in colon secondary to pyloric stenosis or functional obstruction	✔ (Colazal®)	✔ (Asacol®, Asacol® HD, Delzicol®, Lialda®)	-	-
Diarrhea, dose-related; monitor and notify prescriber	-	-	✔	-
Exacerbations of colitis; monitor closely while on therapy; discontinue if symptoms intolerable	✔	✔ (Asacol®, Asacol® HD, Canasa®, Rowasa®, sfRowasa®)	✔	-
Fibrosing alveolitis	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Glucose-6-phosphate dehydrogenase deficiency; monitor for signs of hemolytic anemia and discontinue immediately	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Hepatic impairment; use caution in preexisting dysfunction and monitor routinely	✔ (Giazo®)	✔ (Apriso®, Asacol®, Asacol® HD, Delzicol®, Lialda®, Pentasa®)	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Infertility (males); reversible with drug discontinuation	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Neuromuscular and central nervous system changes, irreversible;	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)

Warnings/Precautions	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
monitor frequently				
Oligospermia; reversible with drug discontinuation	-	✔ (Rowasa®, sfRowasa®)	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Pancolitis; monitor routinely	-	✔ (Canasa®, Rowasa®, sfRowasa®)	-	-
Pericarditis; monitor for signs and symptoms; re-challenge only under careful clinical observation	-	✔ (Canasa®, Lialda®, Rowasa®, sfRowasa®)	-	-
Renal toxicity; use caution in preexisting dysfunction and monitor frequently	✔	✔ (Rowasa®, sfRowasa®)	-	-
Renal impairment (i.e., minimal change nephropathy, acute and chronic interstitial nephritis, renal failure, etc.); use caution in preexisting dysfunction and monitor frequently	-	✔ (Apriso®, Asacol®, Asacol® HD, Delzicol®, Lialda®, Pentasa®)	-	-
Sulfite sensitivity; unknown risk in general population; may require epinephrine treatment	-	✔ (Rowasa®)	-	-
Urine and skin discoloration (orange-yellow); advise patient and monitor	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Undisintegrated passing of tablets; notify prescriber if this continues	-	✔ (Asacol®)	-	✔ (Azulfidine EN-tabs®)

Drug Interactions

Table 9. Drug Interactions[5-18]

Generic Name	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Antacids; dissolution of the granules is pH dependent; avoid co-administration.	-	✔ (Apriso®)	-	-
Cyclosporine; decreased cyclosporine serum levels may be reduced, increasing the risk of nephrotoxicity.	-	-	-	✔
Digoxin; reduced absorption with co-administration; avoid concomitant administration.	-	-	-	✔ (Azulfidine®, Azulfidine EN-tabs®)
Folic acid; reduced	-	-	-	✔

Generic Name	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
absorption with co-administration; avoid concomitant administration.				(Azulfidine®, Azulfidine EN-tabs®)
Heparinoids and low molecular weight heparin; increased risk of bleeding after neuraxial anesthesia; discontinue salicylates before low molecular weight heparin administration, if possible. If unable to discontinue, monitor closely for bleeding.	-	-	✔	-
Methotrexate; displacement of methotrexate from protein binding and decreased renal clearance, increasing the risk of bone marrow suppression; monitor for hematologic toxicity. Also increases gastrointestinal adverse events, especially nausea.	-	-	-	✔
Sulfonylureas; impairment in hepatic metabolism of sulfonylureas or altered plasma protein binding; monitor blood glucose and adjust the sulfonylurea dose as needed.	-	-	-	✔
Thioguanine; increased risk of myelosuppression; monitor blood counts.	-	-	✔	-
Thiopurines (e.g., 6-mercaptopurine and azathioprine); increased risk of myelosuppression due to decrease thiopurine metabolism; use lowest dose possible of each drug and monitor blood levels (e.g., leukopenia).	-	✔ (oral mesalamine products)	✔	✔
Varicella vaccine; increased risk of Reye's syndrome; avoid salicylates for six weeks after vaccine administration.	-	-	✔	-
Warfarin; anticoagulant effects may be decreased;	-	✔ (oral mesalamine products)	-	-

Generic Name	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
monitor routinely.				
Warfarin; potential elevation in prothrombin time; monitor routinely.	-	-	✔	✔

Dosage and Administration

Table 10. Dosing and Administration[5-18]

Generic Name	Adult Dose	Pediatric Dose	Availability
Balsalazide	Treatment of mildly to moderately active UC: Capsule (Colazal®): 2,250 mg three times daily for up to eight weeks Tablet (Giazo®): 3,300 mg twice daily for up to eight weeks	Treatment of mildly to moderately active UC in patients ≥5 to 17 years of age: Capsule (Colazal®): 750 or 2,250 mg three times daily for up to eight weeks	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)
Mesalamine	Induction of remission: Extended-release capsule (Pentasa®): 1,000 mg four times daily Induction of remission in adults with active, mild to moderate UC: Delayed-release tablet (Lialda®): 2,400 or 4,800 mg once-daily with a meal Maintenance of remission of UC: Delayed-release tablet (Asacol®), delayed-release capsule (Delzicol®): 1,600 mg daily in divided doses Treatment of mildly to moderately active UC: Extended-release capsule (Pentasa®): 1,000 mg four times daily Delayed-release tablet (Asacol®), delayed-release capsule (Delzicol®): 800 mg	Safety and efficacy in pediatrics have not been established.	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 400 mg (Asacol®) 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 375 mg (Apriso®) 500 mg (Pentasa®) Rectal enema: 4,000 mg/60 mL unit (Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)

Generic Name	Adult Dose	Pediatric Dose	Availability
	three times daily for six weeks Maintenance of remission of UC in adults: Delayed-release tablet (Lialda®): 2,400 mg once-daily with a meal Extended-release capsules (Apriso®): 1,500 mg daily in the morning Treatment of moderately active UC: Delayed-release tablet (Asacol® HD): 1,600 mg three times daily for six weeks Treatment of mild to moderately active ulcerative proctitis: Rectal suppository (Canasa®): 1,000 mg at bedtime, retained for one to three hours (or longer if possible), for a treatment duration of three to six weeks Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis: Rectal enema (Rowasa®, SfRowasa®): 4,000 mg (one enema) once daily at bedtime, retained for eight hours for three to six weeks based upon symptoms and sigmoidoscopic findings		
Olsalazine	Maintenance of remission of UC in patients who are intolerant of sulfasalazine: Capsule (Dipentum®): 1,000 mg daily in two	Safety and efficacy in the pediatric population have not been established.	Capsule: 250 mg (Dipentum®)

Generic Name	Adult Dose	Pediatric Dose	Availability
	divided doses		
Sulfasalazine	Treatment of mild to moderate UC, and as adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC: Tablet (Azulfidine®), delayed-release tablet (Azulfidine EN-tab®): initial, 3,000 to 4,000 mg/day in divided doses with dosing intervals not exceeding eight hours; maintenance, 2,000 mg/day Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]: Delayed-release tablet (Azulfidine EN-tab®): 2,000 mg daily in two divided doses	Treatment of mild to moderate UC, and as adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC: Tablet (Azulfidine®), delayed-release tablet (Azulfidine EN-tab®): initial, 40 to 60 mg/kg/day divided into three to six doses; maintenance, 30 mg/kg/day divided into four doses If gastric intolerance occurs after the first few doses; reduce dose by half and slowly titrate over several days. If intolerance continues; stop drug for five to seven days; then re-introduce at a lower dose. Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs: Delayed-release tablet (Azulfidine EN-tab®): 30 to 50 mg/kg of body weight daily in two divided doses; maximum dose, 2,000 mg per day	Delayed-release tablet: 500 mg (Azulfidine EN-tab®) Tablet: 500 mg (Azulfidine®)

NSAID=nonsteroidal anti-inflammatory drug, UC=ulcerative colitis

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Gastroenterology, Practice Parameters	Management of mild to moderate distal colitis • Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates.

Clinical Guideline	Recommendations
Committee: **Ulcerative Colitis Practice Guidelines in Adults (2010)**[4]	• The combination of oral and topical agents is "superior" to each agent used alone. • Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-analysis demonstrated topical mesalamine to be "superior" to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. • Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. • Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. <u>Maintenance of remission in distal disease</u> • Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. • Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. • Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. • When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. <u>Management of mild-moderate extensive colitis: active disease</u> • Oral sulfasalazine is considered first-line. • Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. • 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. • Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. <u>Maintenance of remission for mild-moderate extensive colitis</u> • Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses. • 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. • Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. <u>Management of severe colitis</u> • If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent hospitalization is not required. • Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. • Failure to significantly improve within three to five days indicates need for

Clinical Guideline	Recommendations
	intravenous cyclosporine (or colectomy - weaker evidence). • Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.

Conclusions

Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. Treatment strategies for IBD management are generally centered on agents that work to relieve the inflammatory process, including agents that inhibit tumor necrosis factors, antimicrobials, corticosteroids, immunosuppressive agents, and salicylates. While all of these agents are used to treat active disease, some are also effective in lengthening the time of disease remission.[1] The oral 5-aminosalicylic acid (5-ASA) derivatives include balsalazide, mesalamine, olsalazine and sulfasalazine. Oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine. Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[20]

Studies conducted with mesalamine have demonstrated an improvement in active, mild to moderate and moderate ulcerative colitis. Moreover, mesalamine treatment also improves clinical response and disease remission rates.[24.25] Once-daily mesalamine appears to be as effective as multiple daily dosing regimens.[29] Topical rectal therapies are the drugs of choice for distal disease and are more effective than oral sulfasalazine therapy.[36] Rectal 5-ASA therapy has been shown to be more effective compared to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not more effective compared to oral 5-ASA for symptomatic improvement.[39] Topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis.[27,38]

According to the American College of Gastroenterology guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. Topical mesalamine agents are more effective than topical steroids or oral aminosalicylates. Combination therapy with oral and topical agents is more effective than each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone.[4] Sulfasalazine is considered a first-line treatment in the management of mild to moderately active colitis. Moreover, balsalazide, mesalamine, olsalazine and sulfasalazine are effective for reducing the number of relapses and the maintenance of mild to moderate disease remission.[4] The differences in drug therapies (i.e., pH-dependent parameters) allow treatment to be tailored based upon an individual's disease location and severity.

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